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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,259	02/23/2001	Madhav N. Devalaraja	PC18174A	3713

7590

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EXAMINER

BELYAVSKIY, MICHAEL A

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,259	DEVALARAJA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskiy	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12, 14, 31, 33-34, 36-37, 39, 41-42 and 44 - 50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12, 14, 31, 33-34, 36-37, 39, 41-42 and 44 - 50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/28/04 has been entered.

Claims 12, 14, 31, 33-34, 36-37, 39, 41-42 and 44 - 50 are pending.

In view of the amendment, filed 6/12/02(Paper No. 13), the following rejection remains

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 12, 14, 31, 33-34, 36-37, 39, 41-42 and 44 - 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) a method for screening for an inhibitors of a CSF and M-CSF in *in vitro* assays based on inhibition of chemoattraction and/or accumulation and /or activation of leukocytes by CSF and; 2) *in vivo* recruitment assay response to IL-8, using rabbit as animal model, does not reasonably provide **enablement** for: 1) a method of treating inflammation, such as sepsis, or osteoporosis, an autoimmune disease or atherosclerosis, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 12 and 14, or 2) a method of treating inflammation, such as psoriasis or asthma, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 31, 37 and 42 or 3) a method of treating rheumatoid arthritis in a mammal comprising administering an antibody to M-CSF, claimed in Claims 34 and 50. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, Paper No: 10, mailed 07/28/03

Applicant's arguments, filed 01/28/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the claims, as amended are sufficiently enabled under 35 U.S.C. 112, first paragraph and cited references by Campbell et al, wherein administration of an anti-M-

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CSF antibody in a mouse CIA model reduced the severity of established CIA and Williams et al. wherein administering of anti-TNF α monoclonal antibody results in reduction in mouse CIA model.

Contrary to Applicant's assertion, the issue raised in the previous Office Action was that the specification does not adequately teach how to effectively treat inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis, by administering an effective amount of an antibody to M-CSF. Moreover, no animals were used as model system to effectively treat inflammation, such as sepsis, or osteoporosis, an autoimmune disease or atherosclerosis, or psoriasis, or asthma, or rheumatoid arthritis comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF. Since there is no animal model system in the specification to effectively treat inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis, by administering to a mammal a therapeutically effective amount of an antibody to M-CSF, it is unpredictable how to correlate *in vitro* results with *in vivo* use. The references provided by Applicant, for example Williams et al. only teach the use of neutralizing anti-TNF-alpha monoclonal antibody to ameliorate arthritis in mice model with type II collagen-induced arthritis. However, Williams et al., stressed that conformation of the importance of possible modes of therapy and treatment in humans can only come from studies from the amelioration of human rheumatoid arthritis (see page 9788 in particular). Similarly, Campbell et al. only teach that administration of an anti-M-CSF antibody in a mouse CIA model. However, Campbell et al. teach that little is known whether endogenous M-CSF is required for disease development and further that caution should be taken in administering treatment to arthritis patients (see pages 144 and 149 in particular). Moreover, in the other publication Campbell et al. (J. of Immunol. 1998, v.1998, pages 3639-3644) teach that the approaches that used the inhibitors of a CSF or receptor antagonists of the cytokines to develop the methods of treating inflammation have several limitations such as: 1) the inhibitors of CSF, including monoclonal antibody may not be accessible to the site of the action; 2) there may be reduced efficacy of the neutralizing antibody due to an immune response to this foreign protein (see Discussion overlapping pages 3642-3643 in particular). Mestas et al. (J. of Immunology, 2004, 172, pages 2731-2738) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasingly important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Feldman et al. (IDS) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al. further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Aoki et al. (US Patent 5,470,578) teach that the cause of a chronic multiple inflammatory disease,

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rheumatoid arthritis, is still unknown and no reliable treatment of the disease has been established (see entire document, column 1, lines 55-60 in particular). Since the method of treating inflammation, by administering to a mammal a therapeutically effective amount of an antibody to M-CSF can be species- and model-dependent (see Van Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treating inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis by administering to a mammal a therapeutically effective amount of an antibody to M-CSF . Moreover, Applicant himself acknowledge that the ability of CSF to synergistically enhance the chemoattractant effects of chemokines on recruitment of leukocytes to sites of inflammation was unexpected (page 4, line 8 of the Specification as filed) . As such, the invention must be considered unpredictable.

The specification does not provide sufficient teaching as to how it can be assessed that treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis was achieved after the administration of a therapeutically effective amount of an antibody to M-CSF. Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis, comprising administering an effective amount of a therapeutically effective amount of an antibody to M-CSF in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

3. No claim is allowed


4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskiy whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 5, 2004


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